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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/281,717	03/30/99	BAXTER J	UCAL-253/02U

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EXAMINER	
MORAN, M	
ART UNIT	PAPER NUMBER
1631	11

DATE MAILED: 10/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Offic Action Summary	Application No.	Applicant(s)	
	09/281,717	BAXTER ET AL.	
	Examiner	Art Unit	
	Morjorie Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Prosecution Application

The request filed on 7/3/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/281,717 is acceptable and a CPA has been established. An action on the CPA follows. No preliminary amendment was filed with the CPA and no amendments or arguments regarding rejections set forth in the office action of 12/13/00 have been received as of the date of this office action.

Specification/Priority/Declaration

In view of the new declaration filed 1/26/01, the objection to the declaration/oath is hereby withdrawn.

Claim Rejections - 35 USC § 112

Claim 16 is again rejected, as previously set forth in the office action of 12/13/00, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Applicant has not filed any arguments or amendments in response to the office action of 12/13/00, therefore the rejection is maintained. The text of the rejection is repeated below for applicant's convenience.

Amended claim 16 newly recites the term "nuclear receptor box motif". Neither the term "nuclear receptor box" nor the phrase "nuclear receptor box motif" is taught or recited anywhere in the originally filed specification or claims. Original claim 16 recited an "NR-box". The specification recites various NR-boxes comprising motifs. For example, page 14 of the originally filed specification teaches SEQ ID NO: 1 with an LxxLL motif of an NR-box 2 peptide. Figure 7 also describes NR-boxes and an NR box, which are presumably involved in "Nuclear Receptor Interactions", as indicated by one of the figure titles, but nowhere is the term "NR" defined as "nuclear receptor", and nowhere is the term "nuclear receptor box" actually recited. Further, the phrase nuclear receptor box motif" is not taught anywhere. For these reasons, claim 16 is rejected for containing new matter.

Claims 1-17 and 30 are again rejected, as previously set forth in the office actions of 6/14/00 and maintained in the office action of 12/13/00, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying compounds which modulate coactivator binding to nuclear receptors with cofactor (coactivator) binding sites, does not reasonably provide enablement for a similar method wherein nuclear receptors do not have coactivator binding sites (i.e. any nuclear receptor or nuclear receptors not known to have coactivator binding sites). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments filed 9/20/00 have been fully considered but they are not persuasive, for reasons previously set forth. Applicant has not filed any further arguments in response to the rejection set forth in the office action of 12/13/00. The response to arguments filed 9/20/00 are repeated below for applicant's convenience. In response to the argument that

nuclear receptors appear to have conserved ligand binding domains based on sequence homology, it is noted that sequence homology (and structural predictions based thereon) merely suggest similar functions and are not necessarily predictive. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the teaching of homologous structural domains is not a teaching for predictability with regard to coactivator binding. The specification therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981{1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. In response to the argument that the specification teaches how to determine if a receptor binds coactivators and that such experimentation would be "routine", it is noted that applicant has thereby admitted that experimentation would indeed be necessary to determine if a particular receptor is one to which coactivators bind, and that such experimentation would be required before the claimed methods may be successfully performed. Given the large number of nuclear receptors known in the art, and given that ligands have not yet been identified for some of those receptors (i.e. "orphan" receptors), the examiner maintains that it would require undue experimentation to determine (a) if a particular nuclear receptor (e.g. one for which a coactivator is not known in the art) actually binds to a coactivator, (b) the identity of the coactivator(s) (if there is/are any); and (c)

how to measure modulation of binding between the identified coactivator and its receptor. The guidance given by the instant specification teaches general methods for measuring modulation of binding (i.e. competition assays) for KNOWN coactivators and receptors. However, also as taught by the specification and by the prior art (see e.g. RIBEIRO *et al.*, Recent Prog. Hormone Ther. (1997), page 369) some coactivators are known to bind to receptors in synergy with ligands, and may therefore bind poorly or not at all to a receptor in the absence of its ligand. It would therefore be necessary for one skilled in the art to determine what factors are necessary for "normal" binding of a cofactor and/or to determine under what conditions binding would be considered "normal" (e.g. pH, salt concentrations, presence of ions, etc.) before being able to determine whether any compound is able to modulate binding of the coactivator to its receptor in a competition-type of assay. The specification also gives guidance for methods of measuring binding modulation by measuring transcription activation. Again, one skilled in the art would first have to determine what nucleic acids (e.g. genes) are transcribed by a particular factor, and what the level of transcription is in the presence of a receptor with and without a coactivator before being able to measure whether a particular compound affects the transcription level. For the reasons set forth above, the examiner maintains that it would require undue experimentation for one skilled in the art to determine how to "use" the claimed method wherein the receptor is not known to bind coactivators.

Claims 1-17 and 30 are again rejected, as previously set forth in the office action of 12/13/00, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has not filed any arguments or amendments in response to the office action of 12/13/00, therefore the rejections are maintained. The text of the rejections are repeated below for applicant's convenience.

Claim 1 recites a method of screening for a compound which modulates binding of a coactivator to a nuclear receptor in lines 1-2, then recites steps of modeling test compounds and screening for binding of a test compound to a particular binding site on a receptor. Claim 1 does not recite any step of measuring modulation of *coactivator* binding. In fact, claim 1 does not recite any measurement or indication of coactivator binding to anything. Examples of methods to measure modulation of coactivator binding by a test compound are recited in the specification, (e.g. competitive binding, transcription activation) as argued by applicant in the response filed 9/18/00, therefore methods to measure modulation of coactivator binding to a receptor are enabled. However, in the absence of a step or steps reciting measurement of modulation of coactivator binding by a test compound, claim 1 merely recites a method to measure binding of a test compound to a receptor. As a step to measure modulation of binding of a coactivator to a receptor is not recited in the claim, it is unclear whether the claim is merely directed to a method of screening for compounds which bind to a receptor, as indicated by the recited steps, or is directed to a method of identifying a compound which modulates binding between a coactivator and its receptor, as indicated by the preamble, and the claim is indefinite.

Claim 17 recites a method for identifying an agonist or antagonist of coactivator binding in lines 1-2, then recites steps of modeling compounds and binding the compounds to a coactivator binding site. As in claim 1, there is no recitation of a step for measuring coactivator binding or modulation thereof. As set forth above, the specification does teach correlation of transcription activation with binding of a coactivator to a receptor, and teaches that compounds

which modulate binding of a coactivator to its receptor can be identified, thereby enabling claim 17. In the absence of a step of measuring modulation of coactivator binding to its receptor, it is unclear if the claim is directed to a method of measuring binding of a compound to a receptor site, as indicated by the recited claims, or is directed a method of identifying a compound which acts as an antagonist or agonist on binding between a coactivator and its receptor, and the claim is indefinite. In addition, the examiner interprets an "antagonist" of coactivator binding to be a compound which blocks binding, and an "agonist" of binding to be one which increases binding of a coactivator to its receptor. Applicant is warned that if these are the meanings intended by applicant, then claims 1 and 17 are coextensive in scope, and if claim 1 is allowed, claim 17 will be rejected as being a substantial duplicate thereof. It is further noted that although "antagonist" and "agonist" usually refer to an activity (e.g. of a receptor) and not merely to binding, the instant claim recites "an agonist or antagonist of coactivator binding to a nuclear receptor", therefore the "agonist" or "antagonist" function of the compound identified is interpreted to be limited to that which affects binding between a coactivator and a nuclear receptor ONLY; and is not interpreted as antagonism or agonism of receptor function itself.

Claim 12 recites the term "biological assay". Applicant argues that this term is defined on pages 15-16. The specification, however, does not explicitly define the term, but teaches on page 15, lines 28-34 that screening assays may be performed *in vitro* or *in vivo*, and teaches that preferred "biological screening" includes activity-based response models, binding assays, and assays in particular cell lines, wherein the cell assays are those which measure the biological effect of a compound in a cell. The term "biological assay" is often interpreted in the art to refer to *in vivo* assays only, but is sometimes interpreted to refer to any assay wherein "living" systems are used (e.g. *in vitro* cell-based assays). Based on the teachings of the specification, it appears that applicant intends the latter; however, this is not explicitly set forth

anywhere. In addition, "binding assays" encompass both cellular binding and noncellular binding (e.g. to purified receptors), therefore not all binding assays are considered "biological" assays in the art. Further, mere binding to a receptor (or inhibition thereof, or competition therefore), in the absence of any other "biological" effect on the cell (e.g. endocytosis, activation of transcription, downregulation of protein synthesis, etc.) is not necessarily considered a "biological" assay in the art. As there are a plethora of meanings in the art for the term "biological assay", as set forth above, and as the specification does not explicitly set forth applicant's intended meaning, it is unclear what limitations applicant intends by use of the term, and the claim is indefinite.

Claims 2-8 recite the term "corresponding to" which applicant argues means "equivalent to". As previously set forth, "corresponding" presumably refers to a sequence alignment or identity, but no parameters for an alignment or identity are set forth. The term "equivalent to" is equally unclear. The definition argued by applicant does not clarify the metes and bounds of applicant's invention, therefore the rejection of claims 2-8 is maintained.

Claim 16 recites the term "nuclear receptor box motif". For purposes of this rejection, the examiner interprets "nuclear receptor box" to be equivalent to the originally recited term "NR-box". Neither an NR-box nor an NR-box motif are specifically defined by the specification or claims, therefore the claim is indefinite. In addition, the multiple identification of NR-boxes 1, 2, and 3 make it unclear what applicant considers to be NR-box 1, 2, or 3, therefore it is unclear what applicant considers to be the metes and bounds of his invention. Page 6 of the specification refers to NR-boxes depicted in the figures. Only Figure 7 actually shows a "definition" (i.e. sequence or physical structure) of NR-boxes. NR-box 1 appears to consist of residues 15-21 of either SEQ ID NO: 5 or SEQ ID NO: 6. As SEQ ID NO's 5 and 6 are not identical, it is unclear which sequence actually represents NR-box 1. NR box 3 appears to

consist of residues 15-21 of SEQ ID NO: 7. However, the specification teaches that an NR-box 2 peptide comprises residues 11-23 of SEQ ID NO: 6 and an NR-box 3 peptide comprises residues 9-21 of SEQ ID NO: 7. On page 33, NR-box 3 is defined as residues 12-17 or residues 8-24 or residues 5-24 of SEQ ID NO: 7 and NR-box 2 is variously defined as residues 15-20, or residues 11-23 or residues 7-23 of SEQ ID NO: 6. It is therefore unclear whether SEQ ID NO: 6 is intended to represent NR-box 1 or NR-box 2 (or both). It is also unclear what portions of the SEQ ID's actually represent NR-boxes. In addition, nowhere is an NR-box motif specifically defined. Page 33, line 16 appears to defined a "minimal motif" of NR-box 3. However, a teaching for a "minimal motif" implies that other, non-minimal "motifs" exist and are possible. No motifs are taught for NR-boxes 1 or 2. As it is unclear what sequence or sequences are intended by applicant by a "nuclear receptor box" or by a "nuclear receptor box motif", the claim is deemed unsearchable and will not be further considered on its merits.

Claim Rejections - 35 USC § 102

Claims 1, 10, 12-15, 17, and 30 are again rejected, as previously set forth in the office actions of 6/14/00 and 12/13/00, under 35 U.S.C. 102(b) as being anticipated by SCANLAN *et al.* (WO 97/221993).

Applicant's arguments filed 9/20/00 have been fully considered but they are not persuasive, for reasons previously set forth. Applicant has not filed any further arguments or amendments in response to the office action of 12/13/00, therefore the rejection is maintained. The text of the rejection is repeated below for applicant's convenience.

In response to the argument that SCANLON tests the ability of a bound ligand to modulate the binding of the coactivator protein, which applicant argues is NOT the invention, applicant is reminded that the claims are drawn to a method of identifying ANY compound which

modulates binding of a coactivator to the receptor. SCANLAN teaches that ligand binding domains of nuclear receptors comprise an activation domain which can be modulated by binding of a ligand to the domain, and further teaches that ligands may be designed which disrupt binding of contact of the domain (to/with any other molecule), thus acting as an antagonist or agonist (page 26, lines 13-18). SCANLAN's teaches modeling of his entire ligand domain (which comprises a coactivator domain) and compounds which bind therein, as previously set forth, which is inherently a teaching for modeling of the coactivator domain and identification of compounds which modulate binding to the coactivator domain. Congruently, his teaching that his ligands modulate binding to the activator domain (i.e. coactivator binding domain) is inherently a teaching for modulation of binding to the coactivator domain. The examiner therefore maintains that SCANLAN anticipates all of the limitations of the claims. It is noted that applicant admits on page 10 of the response filed 9/20/00 that SCANLAN tests the ability of a ligand (bound to the receptor) to modulate the binding of a coactivator protein. The argument that the ligands of SCANLAN are known is irrelevant, as the claims are not limited to modeling of unknown compounds only. For the reasons set forth above, the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 1-9, 10, 12, 14-15, 17 and 30 are again rejected, as previously set forth in the office action of 12/13/00, under 35 U.S.C. 103(a) as being unpatentable over SCANLAN *et al.* (WO 97/21933) in view of COLLINGWOOD *et al.* (IDS document: PNAS 94, pp. 248-253 (1997)).

Applicant has not filed any arguments or amendments in response to the office action of 12/13/00, therefore the rejection is maintained. The text of the rejection is repeated below for applicant's convenience.

Claim 1 recites a method of identifying a modulator of coactivator binding to a nuclear receptor wherein test compounds are modeled "using" an atomic structural model of a nuclear receptor's coactivator binding site or a portion thereof, then are screened for binding to a nuclear receptor coactivator binding site, and thus identified as modulators. Claims 2-4 limit the structural model to comprise coordinates for specific amino acid residues. Claims 5-8 limit the coactivator binding site to comprise specific amino acids "corresponding" human thyroid receptor residues. Claim 9 limits the receptors to specific types. Claim 10 limits the screening to in vitro methods. Claim 12 limits the assay to be biological. Claim 14 limits the test compound to be an agonist or antagonist of coactivator binding. Claim 15 limits the test compound to be a small organic molecule, peptide or peptidomimetic. Claim 17 recites a method to identify an agonist or antagonist of coactivator binding to a nuclear receptor wherein the atomic coordinates of a coactivator binding site of a receptor are provided to a computerized modeling system, (test) compounds are modeled, and identified by binding.

SCANLAN teaches a method to identify compounds which modulate binding to a coactivator site of the thyroid receptor, wherein his compounds may act as agonists or antagonists, as set forth above. SCANLAN's compounds are peptides (p. 53), and the receptor modeled by SCANLAN is a thyroid receptor (see Figures 21-26B). SCANLAN does not teach modeling of the specific residues recited in the claims.

COLLINGWOOD teaches that leucine 454 (Leu454) is found in the coactivator binding domain (AF-2), and teaches that mutation of this residue interferes with or abolishes binding of coactivators (e.g. RIP140) to the receptor (p. 250, right column).

It would have been obvious to one of ordinary skill in the art at the time of invention to have included molecular coordinates for COLLINGWOOD's residue Leu454 in the model and method of modulation of ligand binding of SCANLAN where the motivation would have been to include a residue known to be critical in ligand and coactivator binding and associated activity (activation) of the receptor, as suggested by COLLINGWOOD. One skilled in the art would reasonably have expected success in including coordinates for Leu454 in the model of SCANLAN's method because SCANLAN has successfully modeled all of the ligand binding domain, which includes the coactivator binding domain, and COLLINGWOOD teaches that the position of Leu454 in the crystal structure of a thyroid receptor is known (p. 248, right column).

Claims 1, 10, 11-13, 15, 17 and 30 are again rejected, as previously set forth in the office actions of 6/14/00 and 12/13/00, under 35 U.S.C. 103(a) as being unpatentable over SCANLAN *et al.* (WO 97/21933) in view of KUNTZ *et al.* (IDS document: Science 257, pp. 1078-1082. (1992)).

Applicant's arguments filed 9/20/00 have been fully considered but they are not persuasive, for reasons previously set forth. Applicant has not filed any further arguments or amendments in response to the office action of 12/13/00, therefore the rejection is maintained. The text of the rejection is repeated below for applicant's convenience.

Applicant reiterates the arguments regarding the deficiencies of SCANLAN and has not set forth any further arguments under 35 USC 103 regarding the obviousness of claims 1, 10, 11-13, 15 and 17. The examiner maintains that SCANLAN teaches a method to identify compounds which modulate or act as agonists or antagonists to binding of a coactivator to its receptor site, and that SCANLAN teaches compounds so identified, as set forth above. The

examiner therefore also maintains that SCANLAN in view of KUNTZ make obvious the claims for the reasons and motivations previously set forth.

Conclusion

Claims 1-17 and 30 are again rejected, claims 18-29 are again withdrawn.

This is a CPA of applicant's earlier Application No. 09/281,717. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Patent Analyst, Dianiece Jacobs whose telephone number is (703) 305-3388.

Marjorie A. Moran
October 15, 2001

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
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